Express Mail: EL560[redacted]

525 Rec'd PCT/PTO 10 OCT 2000

FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF [redacted]MERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: HASLP004

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): 09/673074

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/01066	7 April 1999	7 April 1998

TITLE OF INVENTION

OCULAR IRRIGATING SOLUTION

APPLICANT(S) FOR DO/EO/US

ARMITAGE, William, J. and YAGOUBI, Mohamed, I.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

Express Mail: EL560313906US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/673074	PCT/GB99/01066	HASLP004

21. The following fees are submitted:.

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BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1,000.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	$860.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$0.00 | $860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00 |

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	11 - 20 = 0	0	x $18.00	$0.00	0
Independent claims	2 - 3 = 0	0	x $80.00	$0.00	0
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$0.00	0
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐	$0.00	
SUBTOTAL =				$0.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00	
TOTAL NATIONAL FEE =				$0.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00	
TOTAL FEES ENCLOSED =				$0.00	$860.00
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of $860.00 to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 50-0388 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

BEYER WEAVER & THOMAS, LLP
P.O. BOX 778
BERKELEY, CA 94704-0778

22434

PATENT TRADEMARK OFFICE

SIGNATURE

Jeffrey K. Weaver
NAME

31,314
REGISTRATION NUMBER

October 10, 2000
DATE

10-10-45 09/673074
525 Rec'd PCT/PTO 04 OCT 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this paper and the documents and/or fees referred to as attached therein are being deposited with the United States Postal Service on October 04, 2000 in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR §1.10, Mailing Label Number EL560313937US, addressed to the Assistant Commissioner for Patents, Washington, DC 20231.

Nidhi Khanna

Nidhi Khanna

Attorney Docket No.: HASLP004

First Named Inventor: Armitage

TRANSMITTAL LETTER FOR A PCT INTERNATIONAL APPLICATION ENTERING THE NATIONAL STAGE IN THE U.S. AS A DESIGNATED or ELECTED OFFICE UNDER 35 USC 371

Assistant Commissioner for Patents
Box PCT
Attention: DO/EO
Washington, DC 20231

☐ Duplicate for fee processing

Transmitted herewith are the papers required to enter the national stage in the U.S. as a designated office/elected office for the following PCT international patent application:

INTERNATIONAL APPLICATION NUMBER: PCT/GB99/01066
Int'l Filing Date: April 7, 1999
1st Priority Date: April 7, 1998
Inventor(s): William John Armitage and Mohamed Ibrahim Yagoubi
For: OCULAR IRRIGATING SOLUTION

The United States Patent Office is: (select one)

☐ A Designated Office (No Demand was filed - See 37 CFR 1.494)
☒ An Elected Office (A Demand for Preliminary Examination was Filed - See 37 CFR 1.495)

Enclosures:

☒ A copy of the international application (if this line is not checked, the international application was previously communicated by the International Bureau or the international application was originally filed in the USPTO).
☐ An English Translation of the International Application
☐ A Combined Declaration and Power of Attorney
☐ A copy of amendments made under PCT Article 19
☐ A translation of amendments made under PCT Article 19
☐ A translation of amendments made under PCT Article 34 (annexes to the international preliminary examination report)
☐ Verified Statement establishing Small Entity Status under 37 CFR 1.9 and 1.27.
☐ Information Disclosure Statement

- ☐ An Assignment of the Invention to: (with $40.00 recordal fee)
- ☒ A Preliminary Amendment
- ☒ A copy of the International Search Report
- ☒ A copy of the Preliminary Examination Report

Fee Calculation:

☐	BASIC FEE (IPEA-U.S. $690/345; ISA-U.S. $710/355; PTO not ISA or IPEA $1000/500; U.S. IPEA all claims meet 33(2)-(4) $100/50; File w/ EPO or JPO search report $860/430;)				$
☐	Surcharge for filing a late oath or declaration ($130/65)				$
☐	Surcharge for filing a late translation ($130)				$
☐	Assignment recordal fee ($40)				$
☐	Multiple dependent claims ($270/135)				$
☐	Excess claims - see calculation below				$
	Total Claims:	- 20 = 0	X $18/9 claim =		$
	Independent Claims:	- 3 = 0	X $80/40 ind. claim =		$
			Excess Claim Total		$
			TOTAL FEES		**$**

☒ **PLEASE DEFER THE FILING FEES AT THIS TIME**

☒ The Commissioner is authorized to charge any fees beyond the amount enclosed which may be required, or to credit any overpayment, to Deposit Account No. 50-0388 (Order No. HASLP004).

General Authorization for Petition for Extension of Time (37 CFR §1.136)

☒ Applicants hereby make and generally authorize any Petitions for Extensions of Time as may be needed for any subsequent filings. The Commissioner is also authorized to charge any extension fees under 37 CFR §1.17 as may be needed to Deposit Account No. 50-0388 (Order No. HASLP004).

☒ Please send correspondence to the following address:

Customer Number 022434
BEYER WEAVER & THOMAS, LLP
P.O. Box 778
Berkeley, CA 94704-0778
Telephone (510) 843-6200
Fax (510) 843-6203

Date: October 4, 2000

Jeffrey K. Weaver
Registration No. **31,314**

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Armitage	Attorney Docket No.: HASLP004
Application No.: Please assign	Examiner: Not assigned
Filed: Herewith	Group: Not assigned
Title: OCULAR IRRIGATING SOLUTION	

Preliminary Amendment

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to an examination on the merits, please enter the following amendments:

In the Claims:

Please cancel claim 12.

In Claim 3, please replace "claim 1 or 2" with --claim 1--.

In Claim 5, please replace "any preceding claim" with --claim 1--.

In Claim 6, please replace "any preceding claim" with --claim 1--.

In Claim 8, please replace "any preceding claim" with --claim 1--.

In Claim 9, please replace "any preceding claim" with --claim 1--.

In Claim 11, please replace "any one of claims 1 to 9" with --claim 1--.

REMARKS

Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

Jeffrey K. Weaver
Reg. No. 31,314

P.O. Box 778
Berkeley, CA 94704-0778

OCULAR IRRIGATING SOLUTION

This invention relates to aqueous solutions for use in surgical procedures, and is particularly concerned with an ophthalmic irrigating solution useful for irrigating the human eye during surgery.

A description of the problems associated with surgical procedures, especially surgical procedures performed on the eye, and the historical development of tissue irrigating solutions may be found in EP-A-0076658.

The stated object of EP-A-0076658 is to provide a stable sterile ophthalmic irrigating solution which, in addition to correct electrolyte balance, provides factors necessary for continued metabolism in the endothelial cells, maintenance of the fluid transport pump system, and consequential maintenance of proper corneal thickness and clarity. This problem is stated to be achieved in EP-A-0076658 by providing a two-part solution system which includes a basic solution and an acidic solution which are individually stable and which, on mixing, form an ocular solution which contains the necessary factors to maintain endothelial cell integrity and corneal thickness during ocular surgery. The combined solution contains the necessary ions in a bicarbonate-phosphate buffer as well as oxidised glutathione and dextrose (d-glucose), the latter being present as an energy source.

There are problems associated with the solution system of EP-A-0076658. Firstly, such a system is relatively expensive because two separate solutions must be prepared and separately sterilised; this problem is not easy to overcome because certain of the ingredients of the system, particularly the oxidised glutathione and the glucose, are heat-labile and cannot therefore be sterilised by an autoclaving procedure as required by various regulatory authorities for

solutions exceeding about 500ml in volume which are to be used in surgical procedures. As a consequence, the two-part system of EP-A-0076658 is prepared, in practice, such that the non-labile components are present in the solution which contains the majority of the fluid which will form the final ocular solution, which is then bottled and autoclaved. The labile components are contained in the other solution of relatively small volume (below the threshold above which autoclaving is required) which may be sterilised by a filtration technique.

A second problem with the solution system of EP-A-0076658 is that its two-part nature can potentially lead to errors in forming the final ocular solution, a procedure which is normally conducted in a hospital.

HEPES has been proposed, in the 1980 article "Intraocular irrigating and replacement fluid", M.V. Graham et al, Trans. Ophthal. Soc. U.K. (1980) 100, p282-285, as a buffer for an intraocular irrigating solution. However, the 1983 article; "A Comparison of HEPES and Bicarbonate Buffered Intraocular Irrigating Solutions: Effects on Endothelial Function in Human and Rabbit Corneas", by Dayle H. Geroski et al, J. Toxicol - Cut & Ocular Toxicol 1(4), 299-309, (1982-83) concludes that HEPES is toxic to endothelial Na^+K^+ATPase and questions the prudence of using HEPES buffer in intraocular irrigating solutions.

It would be an advantage to provide a stable ophthalmic irrigating solution as a single solution capable of being sterilised by autoclaving.

It has now been found that a solution which is effective as an ophthalmic irrigating solution can be formed which does not require the glutathione ingredient previously believed to be essential, but does include a specific buffer to ensure that the

proper pH is maintained prior to and during use.

Thus, according to a first aspect of the present invention there is provided an ocular irrigating solution for irrigating the eye during surgery comprising, a source of bicarbonate ions and a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0.

The organic buffer preferably maintains the solution at a pH in the range 7.2 to 7.8 to match the physiological pH of 7.4.

Highly preferred as the organic buffer are the zwitterionic amino acids, such as N-2-[hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid], commonly referred to as HEPES, which has a pKa of 7.55 at 25°C. Other organic buffers in this family are N,N-bis[2-hydroxyethyl]-2-aminoethanesulfonic acid (BES), pKa=7.1; 3-[N-morpholino]propanesulfonic acid (MOPS), pKa=7.2 at 25°C; N-tris[hydroxymethyl]methyl-2-aminoethanesulfonic acid (TES), pKa=7.4 at 25°C; N-[2-hydroxyethyl]-piperazine-N'-[3-propanesulfonic acid] (EPPS), pKa=8.0 at 25°C; N-tris[hydroxymethyl]methyl-glycine (TRICINE), pKa=8.1 at 25°C.

The organic buffer should be present in the solution in an amount sufficient to buffer the solution over the duration of the surgical procedure. In practice, this means that the concentration of the buffer should be about 10 to 50 mmol/l.

The bicarbonate source is normally sodium bicarbonate. The bicarbonate source is preferably present in the solution to give a bicarbonate concentration of about 10 to 50 mmol/l, preferably from 15 to 25 mmol/ml to maintain the fluid pump system in the endothelium of the eye.

The ocular irrigating solutions of the present invention are preferably free from glutathione, which

has previously been considered essential for effective performance.

Hitherto it has been considered essential for ocular irrigating solutions to contain an energy source which is purportedly required as a substrate for the various metabolic pathways taking place in the cornea. It has now surprisingly been discovered that ocular irrigating solutions which are free from an energy source (such as glucose) are capable of supporting endothelial function and maintaining corneal thickness as well as solutions containing the energy source. Thus, irrigation solutions of the invention need not contain an energy source. This is of particular significance so far as glucose is concerned which tends to degrade at physiological pH over extended time periods. Therefore, preferred ocular irrigation solutions of the present invention do not contain glucose, or any other energy source which tends to degrade at physiological pH over extended time periods. If an energy source is to be present in an irrigation solution of the invention, a typical concentration is 2-10 mmol/l.

The solution of the invention preferably also contains other electrolytes necessary to maintain physiological function, such as Na^+, K^+, Ca^{2+}, and Cl^-, but not Mg^{2+}, which can lead to the formation of magnesium precipitates in some circumstances. These should be present at concentrations which will permit continued cellular integrity and metabolism. Typically, these electrolytes are present in the following concentrations:

Na^+	130 - 180 mmol/l
K^+	3 - 10 mmol/l
Ca^{2+}	up to 5 mmol/l
Cl^-	130 - 210 mmol/l

Preferably the concentration of Ca^{2+} is at least 0.05 mmol/l, and preferably no more than 0.1 mmol/l.

Moreover, the osmolality should be between approximately 250 - 350 mosmol/kg, preferably 290 - 320 mosmol/kg, to maintain osmotic stability of the cells.

Also normally present in the solution will be a source of phosphate ions, although primarily not for buffering purposes, as in EP-A-00766598, but for normal physiological function. The approximate concentration of phosphate in the solution is normally about 1 mmol/l.

The solution of the invention may be prepared by mixing the components together in aqueous solution, in the desired proportions. It may then be bottled and autoclaved in the normal manner.

One advantage of the invention is that it may be autoclaved without any deleterious effect. For this reason, components which would degrade to a significant extent under the chosen autoclave conditions should be excluded or reduced in amount to a point at which degradation is minimal. Typical autoclave conditions are 121°C for 15 minutes or 134°C for 3 min.

The ocular solution of the invention should preferably be free from nutrients of the type normally present in tissue culture media, namely: amino acids, vitamins, hormones, proteins, growth factors, lipids, nucleosides, minerals.

The solution of the invention may be used in a method of surgery performed on the human eye to replace fluid loss during the operation and to maintain corneal function. Thus according to another aspect of the invention, there is provided an aqueous solution, comprising a source of bicarbonate ions and a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0, for use in a surgical

method, preferably a surgical method performed on the eye.

The invention will now be illustrated by reference to the following Example and drawings in which:

Figure 1A shows the change in corneal thickness during assessment perfusion following 90 minutes exposure to the "UB-M2" solution in accordance with the invention and "BSS Plus";

Figure 1B shows the change in corneal thickness during perfusion with a solution in accordance with the invention "UB-M2" solution and with "BSS Plus".

Example 1

A prior art irrigating solution and an irrigating solution in accordance with the invention were tested in a masked laboratory experiment to evaluate their effectiveness. BSS Plus (which is in accordance with EP-A-0076658) was obtained as a two part system and made up as directed. The composition of these solutions along with those of aqueous humour and BSS are shown in Table 1.

Table 1

	Aqueous humour	BSS	BSS Plus	Invention
Na^+ (mM)	162.9	144.0	160.0	137.2
K^+ (mM)	2.2-3.9	10.0	5.0	5.4
Ca^{2+} (mM)	1.8	4.3	1.0	0.075
Mg^{2+} (mM)	1.1	3.2	1.0	-
Cl^- (mM)	131.6	127.2	130.0	121.2
HCO_3^- (mM)	20.2	-	25.0	20.0
HPO_4^{2-} (mM)	0.6	-	3.0	0.8
SO_4^{2-} (mM)	-	-	-	-
Acetate (mM)	-	28.6	-	-
Citrate (mM)	-	5.8	-	-
Lactate (mM)	2.5-4.5	-	-	-
Glucose (mM)	2.7-3.7	-	5.0	-
Glutathione	1.9 μM	-	0.3 mM	-
HEPES (mM)	-	-	-	20.0
Osmolality (mosmol/kg)	304	302	305	320
pH (20°C)	7.4	7.3	7.4	7.4

Corneas obtained from New Zealand White rabbits (3-4 kg) after an intravenous overdose of pentobarbitone sodium were secured on support rings and perfused as described in J. Physiol 1972; 221: 29-41, "The metabolic basis to the fluid pump in the cornea", Dikstein S. and Maurice DM. The paired corneas from each rabbit were randomly allocated, one to BSS Plus and one to the invention. The allocation was unknown to the person performing the experiment. The epithelial surface was covered with silicone oil to prevent changes in corneal thickness owing to evaporation.

The endothelial surface was perfused at 2.5 ml/h, a pressure of 15 cm H_2O and 35°C. During the first 90 minutes of perfusion, corneas were exposed to the intraocular irrigation solution. This was followed by a further 6 hours of perfusion during which endothelial

function was assessed.

Corneal thickness was measured with an ultrasonic pachymeter (DGH Technologies, Inc), every 30 minutes. The silicone oil was removed briefly to allow the measurements to be made. Each measurement was the mean of readings taken at four different sites of the central cornea.

Changes in corneal thickness during perfusion for 90 minutes with the irrigation solutions are shown in Figure 1A.

Corneal hydration and, thus, thickness are controlled by the endothelium through a pump leak mechanism. Removal of bicarbonate ions from the perfusate suppresses endothelial pump function and causes corneal swelling, although inhibition of the pump is not complete unless CO_2 is also removed from the perfusate. Pump function can be restored and the swelling reversed by returning bicarbonate to the perfusate.

After the 90 minute perfusion with one of the irrigation solutions, endothelial function was, therefore, assessed during a further 6 hours of perfusion with Tissue Culture Medium 199 (TC199). The first 2 hours of perfusion were with TC199 with Earle's salts (Sigma, M3769). This solution contained sodium bicarbonate (26 mmol/l), and should have supported endothelial pump function. Two hours of perfusion with TC199 with Hanks' salts (Sigma, M3274) then followed. This solution did not contain bicarbonate ions and, thus, should have caused corneal swelling, although the solution was not CO_2 free. For the final 2 hours, perfusion with TC199 Earle's was restored and, providing that the endothelium was undamaged, corneas should have thinned. Neither of the TC199 solutions contained phenol red, and their measured osmolalities (Roebling osmometer) were 290 and 288 mosmol/kg,

respectively, for TC199 with Earle's salts and TC199 with Hanks' salts.

Rates of change in corneal thickness both during perfusion with the irrigation solutions and during the three parts of the assessment perfusion were determined by regression analysis. Comparisons were made between groups by t-tests at the 5% level of significance. The results obtained are shown in Table 2 and are also illustrated graphically in Figure 1A.

Table 2

Irrigation solution[a]	Initial 90 min exposure to irrigation solution	Rate of change in corneal thickness ($\mu m/h$)[b] TC199 Earle's 0-2 h	TC199 Hank's[c] 2-4 h	TC199 Earle's 4-6 h
BSS Plus	-5.1(4.3)	+0.02(4.2)	+16.1(1.9)	-13.1(5.3)
Invention	-8.4(3.5)	+1.4 (4.7)	+17.7(2.0)	-13.4(3.7)

[a]Corneas were perfused for 90 minutes with an irrigation solution before the assessment perfusion with TC199.

[b]regression coefficient (SD), n=4: + indicates swelling, - indicates thinning.

[c]TC199 Hanks' does not contain HCO_3^-.

There were no differences at the 5% level of significance in rates of change in thickness between corneas exposed to BSS Plus and those exposed to the irrigating solution in accordance with the invention at any stage of the perfusion.

Example 2

An ocular irrigating solution in accordance with the invention was made up as in Example 1.

Corneas were dissected, mounted on support rings and perfused as in Example 1 except that the corneas were perfused continuously for a period of 7.5 hours with either BSS Plus or the invention. Paired corneas, from a single rabbit, were perfused, one with BSS Plus and the other with the invention. The allocation of

corneas to each solution was randomized and masked from the person performing the perfusion. Regression analysis showed no overall change (at the 5% level of significance) in thickness during the course of the perfusion nor was corneal thickness influenced by the type of irrigation solution (see Figure 1B).

In conclusion, Examples 1 and 2 demonstrate that the invention supports endothelial function at least as well as BSS Plus, despite the absence of components, such as glucose and glutathione, that are considered essential constituents of BSS Plus.

CLAIMS

1. An ocular irrigating solution for irrigating the eye during surgery comprising, a source of bicarbonate ions and a physiologically acceptable organic buffer which is an organic zwitterionic buffer having a buffering capacity within the range pH 6.8 to 8.0.

2. An ocular irrigating solution according to claim 1, wherein the organic buffer maintains the solution at a pH in the range 7.2 to 7.8.

3. An ocular irrigating solution according to claim 1 or 2, wherein the organic buffer is a zwitterionic amino acid.

4. An ocular irrigating solution according to claim 3, wherein the organic buffer is N-2-[hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid].

5. An ocular irrigating solution according to any preceding claim, wherein the concentration of the buffer is from 10 to 50 mmol/l.

6. An ocular irrigating solution according to any preceding claim, wherein the bicarbonate source is sodium bicarbonate.

7. An ocular irrigating solution according to claim 6, wherein the bicarbonate source is preferably present in the solution to give a bicarbonate concentration of about 10 to 50 mmol/l.

8. An ocular irrigating solution according to any preceding claim which does not contain glucose, or any other energy source which tends to degrade at physiological pH over extended time periods.

9. An ocular irrigating solution according to any preceding claim having been sterilised by an autoclaving procedure.

10. An ocular irrigating solution according to claim 1, for use in a surgical method performed on the eye.

11. A method of surgery performed on the human eye in which an ocular irrigating solution according to any one of claims 1 to 9 is employed to replace fluid loss during the operation and to maintain corneal function.

12. An ocular irrigating solution substantially as hereinbefore described, with reference to the accompanying examples.

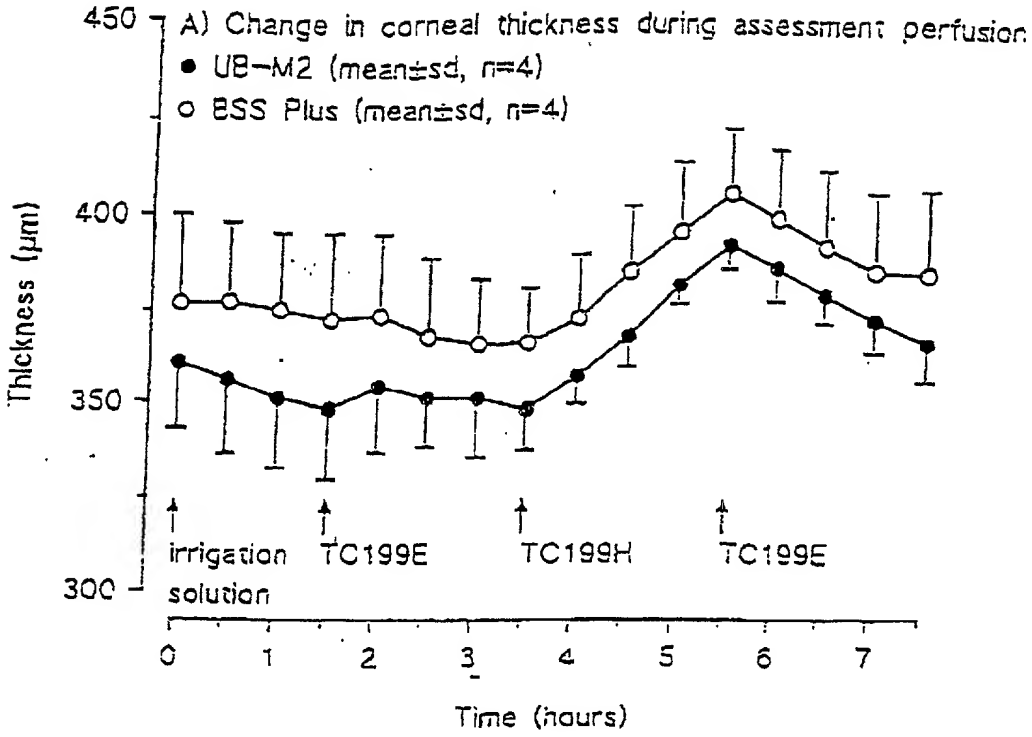

Figure 1A

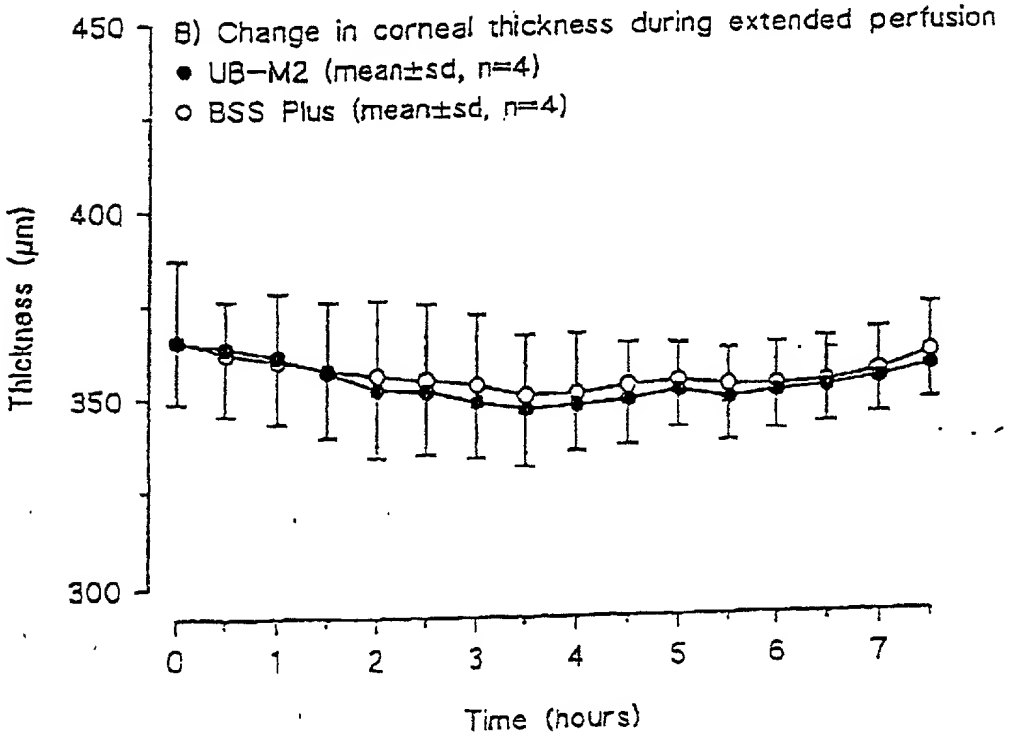

Figure 1B

DECLARATION AND POWER OF ATTORNEY FOR ORIGINAL U.S. PATENT APPLICATION

Attorney's Docket No. HASLP004/HL52257/002/GW/jkl

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: OCULAR IRRIGATING SOLUTION the specification of which,

(check one)

1. ☐ is attached hereto.

2. ☒ was filed on October 10, 2000 as
U.S. Application No. 09/673,074
and was amended on _____.

3. ☐ was filed on _____ as
International PCT Application No. _____
and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, CFR § 1.56.

Prior Foreign Application(s)

I hereby claim foreign priority benefits under Title 35, United States code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

(Application No.)	(Country)	(Filing Date)	Priority Benefits Claimed?
9807491.7	Great Britain	April 7, 1998	Yes X No ___
_____	_____	_____	Yes ___ No ___

Provisional Application(s)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

(Application No.)	(Filing Date)
_____	_____
_____	_____

Prior U.S. Application(s)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application No.)	(Filing Date)	(Status - patented, pending, abandoned)
(Application No.)	(Filing Date)	(Status - patented, pending, abandoned)

Power of Attorney

And I hereby appoint the law firm of **Beyer Weaver & Thomas, LLP** and all practitioners who are associated with the Customer Number 022434 as my principal attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Direct Correspondence To:

Customer Number: 022434
BEYER WEAVER & THOMAS, LLP
P.O. Box 778
Berkeley, CA 94704-0778

22434
PATENT TRADEMARK OFFICE

Direct Telephone Calls To: **Jeffrey K. Weaver at telephone number (510) 843-6200**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Typewritten Full Name of Sole or First Inventor: William John ARMITAGE — Citizenship: United Kingdom

Inventor's signature: W. J. Armitage — **Date of Signature:** 24/11/00

Residence: (City) Avon BRISTOL — (State/Country) Bristol/United Kingdom GBX

Post Office Address: 34 Hutton Close, Westbury-on-Trim, Bristol, Avon United Kingdom BS9 3PT

Second Inventor: Mohamed Ibrahim YAGOUBI — Citizenship: Libya

Inventor's signature: — **Date of Signature:** 24/11/01

Residence: (City) Gloucester — (State/Country) Gloucester, United Kingdom GBX

Post Office Address: 8 Birdlip House, Great Western Road, Gloucester, United Kingdom GL1 3NN